microRNAs-in-liver-and-kidney-ischemia-reperfusion-inju_2021_Biomedicine---P

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ABSTRACT

Ischemia reperfusion injury (IRI) is a condition that occurs wherever blood flow and oxygen is reduced or absent, such as trauma, vascular disease, stroke, and solid organ transplantation. This condition can lead to tissue damage, especially during organ transplantation. Under such circumstances, some signaling pathways are activated, leading to up- or down- regulation of several genes such as microRNAs (miRNAs) that might attenuate or ameliorate this status. Therefore, by manipulating miRNAs level, they can be used as a biomarker for early diagnosis of IRI or suggestive to be therapeutic agents in clinical situation in future.

1. Introduction

Organ transplantation has turn out to be the standard care for the majority of patients suffering from end-stage organ failure. Given the shortage of organs, treatments undoubtedly need to be developed to optimize the quality of available organs in order to attenuate injury to the transplanted organs. In this respect, ischemia has been introduced as an inevitable event, triggering with the cessation of arterial blood flow following organ procurement, post-donation cold ischemia, and warm ischemia during organ transplantation. Accordingly, ischemia-reperfusion injury (IRI) remains to be a life-threatening clinical issue all through procurement, preservation, and surgery, which can even result in higher incidence of acute and chronic rejection as well as long- term morbidity and mortality [1,2]. As an imminent event in organ transplantation, IRI can also activate multiple signaling pathways and subsequently up-regulate several genes, causing cell apoptosis and death and resulting in organ damage [3,4]. In this sense, discovery of small regulatory ribonucleic acids (RNAs) such as microRNAs (miRNAs) has a potential to be employed as a biomarker. In this paper, IRI together with the role of various miRNAs in two major transplanted solid organs, i.e., liver and kidney, affected with IRI, which can ameliorate and/or attenuate this condition, are explained.

1.1. IRI

IRI occurs once blood supply returns to tissues subsequent to a critical time of ischemia or lack of oxygen (namely, hypoxia or anoxia). The blood deprived of oxygen and nutrients during ischemic period can thus create a condition in which circulation restoration results in inflammation and induction of oxidative stress [5]. Moreover, the given condition arises in other clinical situations such as myocardial infarction (MI), stroke, shock, trauma, and peripheral vascular diseases [6–10]. Ischemia also leads to metabolite accumulation, endothelial dysfunction, elevated cell membrane permeability, vascular leak syndrome, as well as interstitial pulmonary edema [11–16]. Although reperfusion is necessary to restore oxygen and nutrients to support cell metabolism and remove potentially damaging by-products of cellular metabolism, it can commence pathogenesis, worsening injuries caused by ischemia *per se*. In addition, short effort of ischemia/reperfusion (I/R) in ischemic preconditioning (IPC) prior to induction of lethal ischemia can activate cell survival program. This further limit post-ischemic injury, indicating that responses to ischemia are bimodal [17].

The mechanisms contributing to the pathogenesis of the IRI condition are multifactorial, complex, and highly integrated. Mechanisms like epithelial-mesenchymal transition (EMT), calcium overload, endoplasmic reticulum stress, mitochondrial dysfunction, toll-like receptor

(TLR) signaling, activated protein kinase (PTK), oxidative stress, inflammation, and apoptosis all are inter-related [18–22]. These incidents are also regulated by miRNAs [23–28]. In fact, miRNAs represent a complex mechanism of genetic regulation that can modulate biological and pathological processes at different levels [29]. The discovery of miRNAs can thus expose entirely new aspects of protein expression [30], considered as a cellular mechanism of short- or long-acting fine-tuning of post-transcriptional gene regulation.

1.2. microRNA & biogenesis

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miRNAs are a subset of short single chain, non-coding RNAs (length of 19–23 nucleotides). They are currently recognized as endogenous physiological regulators of gene expression, which can repress or activate translation/transcription of complementary seed sequences in the 3′- untranslated region (3′-UTR) of target miRNAs. They were first identified in *Caenorhabditis elegans*, as a free-living transparent nematode, in 1993 by Lee et al. These scientists discovered lin-4 that was responsible for regulating timing of larval development through translational repression of lin-14 [30,31]. Since then, over 10,000 miRNAs have been identified in different organisms via random cloning and sequencing [32]. It is of note that miRNAs biogenesis is a multi-stage process. First, miRNAs are transcribed in the cell nucleus from the inter- or intra-genic regions by the RNA polymerase II (RNAPII) to the primitive miRNA form (pri-miRNA) (1–3 kBa in length). Subsequently, these early miRNAs are broken in the nucleus by Drosha as a class 2 ribonuclease (RNase) III enzyme and produce the two-stranded RNA-binding protein called Pasha to stem and loop structures with a length of approximately 70–100 nucleotides, known as pre-miRNA. After transition of pre-miRNAs to the cytoplasm via exportin-5, they are broken down by the Dicer as an RNase III enzyme to two mature-stranded miRNA-miRNA* oligonucleotides with 18–24 bps [33]. Subsequently, separating the two strands from each other, one of them acts as a mature miRNA molecule and it is loaded to the RNA-induced silencer complex (RISC), whereas the other one (passenger miRNA strand) often degrades or plays a functional role in regulating miRNA homeostasis [34] (Fig. 1).

So far, thousands of miRNAs have been detected to target more than 30 % of the genome [32,35,36]. It is noteworthy that a gene can be adjusted by several miRNAs. However, one miRNA might have more than one target based on inadequate pairing [27,37]. In addition, miRNAs are known to play important roles in numerous physiological and pathological processes such as cell cycle regulation, metabolism, signal transduction, and apoptosis [34,35,38,39]. The altered expression of miRNAs is further observed in different clinical conditions such as IRI [37]. Accordingly, gaining more information about miRNAs through improving approaches in functional analysis not only reveals their roles in various cellular mechanisms, but also determines irregular patterns of miRNA expression under these conditions.

1.3. Hepatic IRI

There is a severe shortage of donor livers which has led to the use of

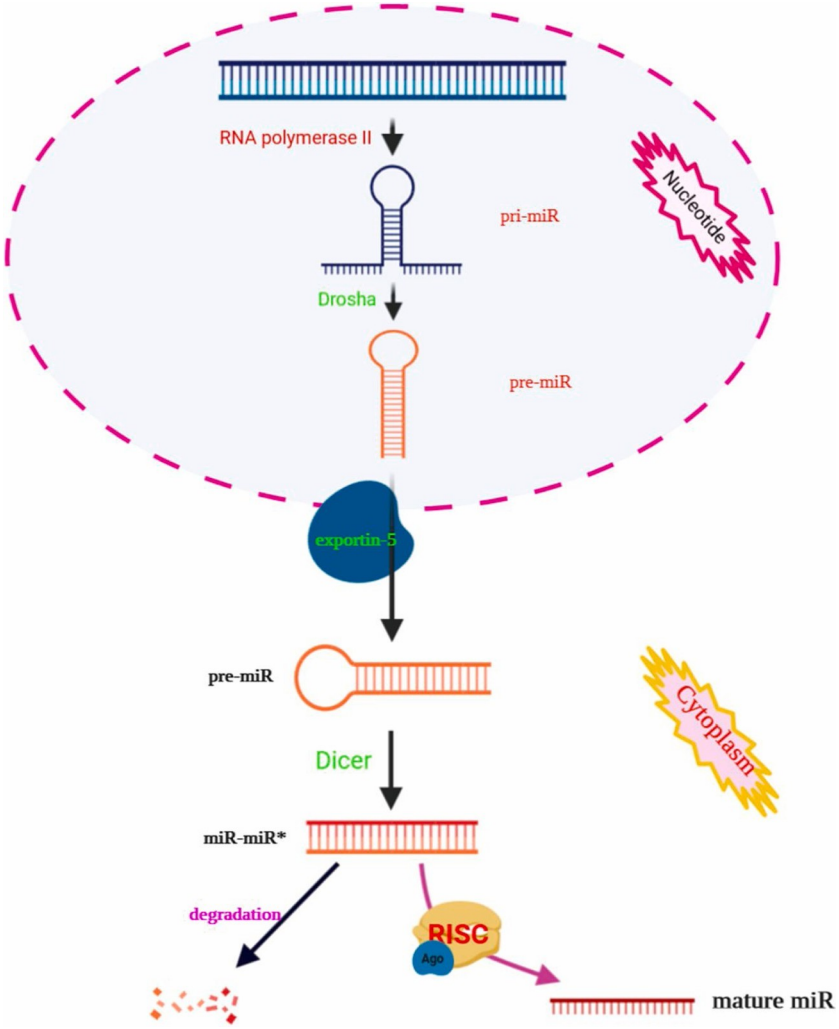

Fig. 1. microRNA biogenesis. Drosha & Dicer as RNase III enzyme, RISC: RNA-induced silencing complex.

prolonged storage of organs or those from non-heart-beating donors. The common feature of these marginal donor livers is high susceptibility to IRI. Hepatic IRI is thus an inevitable problem occurring in major liver resection, liver transplantation surgery, and trauma that can increase early organ failure and incidence of post-transplantation rejection [40–42]. A cascade of physiological and biochemical changes also takes place in hepatic IRI and miRNAs are involved in this pathway [43] (Fig. 2a). Various miRNAs associated with hepatic IRI have been thus far identified, having an influence on this condition (Table 1).

1.3.1. miRNA-370 miRNA-370 expression can be up-regulated in mice subjected to hepatic IRI and its inhibition can lead to down-regulation of serum aminotransferase and pro-inflammatory cytokines, with subsequent improvement of hepatic histological damage. Reporter assays have also confirmed that miRNA-370 can directly target the 3′-UTR of transforming growth factor-b receptor II (TbRII). Moreover, inhibition of miRNA-370 can be sufficient to reinstate the expression of TbRII and its downstream target phosphorylated mothers against decapentaplegic homolog 3, known as SMAD3 [44,45].

1.3.2. miRNA-223 miRNA-223 level can be greatly up-regulated in the liver IRI and correlated with serum markers of ischemic injury. Using prediction assay, acyl-CoA synthetase long-chain family member 3, ephrin A1, and ras-homolog gene family member B (RHOB) can be accordingly predicted to be the downstream targets of miRNA-223 [28].

1.3.3. miRNA-191 miRNA-191 is up-regulated in cultured human liver cell line (LO2) and mice liver tissue during hypoxia-reoxygenation (H/R). In this sense, miRNA-191 deficiency can markedly moderate liver tissue damage, inflammatory cell responses, and cell death in a mouse hepatic IRI model. The activation of miRNA-191 under hypoxic conditions is thus mediated by hypoxia inducible factor-1α (HIF-1α) binding to its promoter region. Upon induction by hypoxia or ischemia, miRNA-191 is also suppressed ZO-1-assolciated Y-box factor (ZONAB) expressions and its downstream factor cyclin D1, resulting in cell death and tissue injury [46–48].

1.3.4. miRNA-182-5p miRNA-182-5p is able to attenuate hepatic I/R by directly suppressing TLR4 and subsequently inhibiting the production of several inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin 6 (IL-6) [49]. TLRs, especially TLR4 and TLR2, have accordingly emerged as putative inducers of the innate immune and inflammatory responses, making them central actors in IRI and cell injury development [50–52].

1.3.5. miRNA-133a-5p
Under H/R condition, miRNA-133a-5p can be upregulated, resulting in an increase in mitogen-activated protein kinase 6 (MAPK6) level as well as promoted cell apoptosis [53]. MAPK signaling pathway can thus regulate the expression of a large number of proteins involved in the control of cell proliferation and differentiation. It is also activated in response to cellular stress such as apoptosis and oxidative injury [54–56].

1.3.6. miRNA-200c miRNA-200c regulates hepatic IRI as it is combined with its target gene zinc finger E-box binding homeobox 1 (ZEB1), involved in hydrogen peroxide (H_2O_2)-induced apoptosis. Inhibition of this miRNA can thus decrease the H_2O_2-induced apoptosis of murine hepatic cell line (AML-12) [57,58].

1.3.7. miRNA-34a
Several studies have established that miRNA-34a has been augmented during stress-induced injuries [59,60]. miRNA-34a is also known as a direct target of p53, inhibiting cell proliferation [61,62]. It

Table 1
microRNA alteration in liver IRI.

miRNAs	Change in IRI	Target(s)	Effect on condition	References

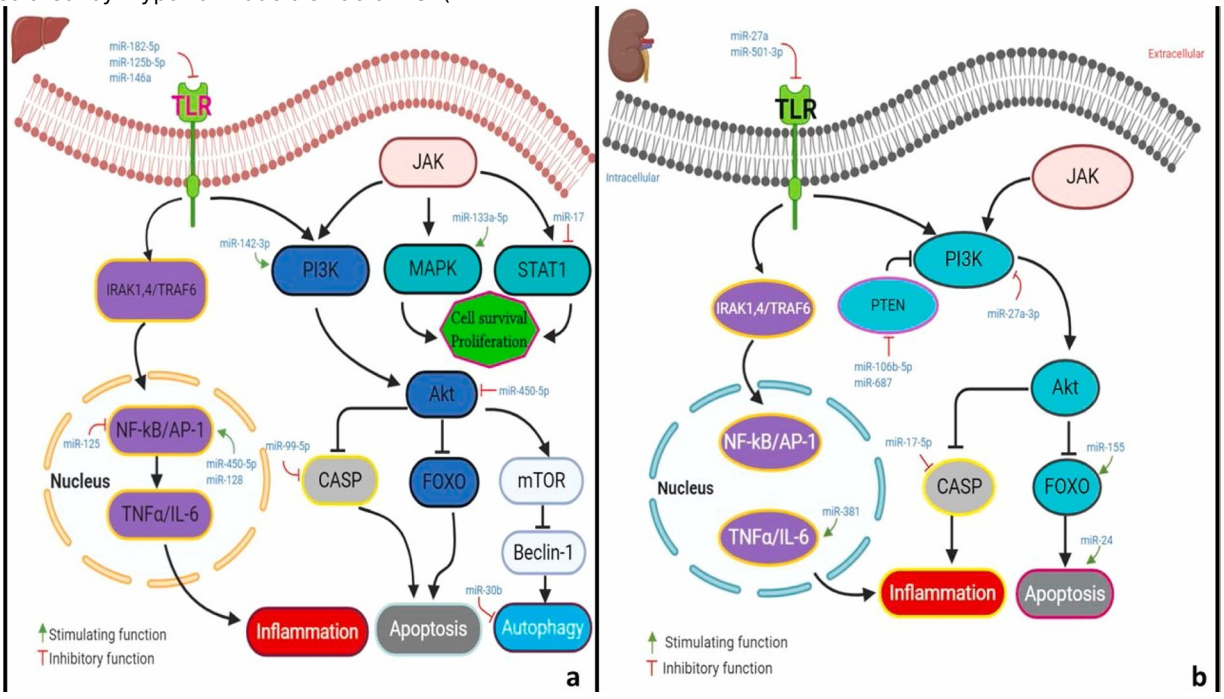

Fig. 2. Pathways involved in IRI with related miRNAs Which ameliorated or worsen this condition in liver "a", and in kidney "b". TLR: Toll like receptor, JAK: Janus Kinase, PI3K/Akt: Phosphatidylinositol 3-kinase/protein kinase B, MAPK: Mitogen-Activated Protein Kinase, STAT: Signal Transducer and Activator of Transcription, CASP: Caspase, FADD: Fas Associated Via Death Domain, PTEN: Phosphatase and tensin homolog, NF-κB: Nuclear factor kappa B, AP: Activator Protein, mTOR: mammalian target of rapamycin, FOXO: Forkhead box O, IRAK: IL-1 receptor-associated kinases, TRAF: TNF receptor associated factor, TNF: Tumor Necrosis Factor, IL: Interleukin.

146a	Down-regulated	TLR, NF-κB	Worsened	[81
30b	Down-regulated	Atg12	Worsened, Autophagy	[83]
200c	Up-regulated	ZEB1	Worsened, Apoptosis	[57,58]
34a	Up-regulated	P53, Nrf2	Worsened	[63,64]

TbRII: Transforming growth factor-b receptor II, ACSL3: acyl-CoA synthetase long chain family member 3, RHOB: Ras Homolog Family Member B, ZONAB: ZO-1-assolciated Y-box factor, JNK: c-Jun N-terminal kinases, Atg12: autophagy related 12, ZEB : zinc finger E-box binding homeobox 1, Nrf2: nuclear factor- erythroid 2-related factor-2, TLR: Toll like receptor, PI3K/Akt: Phosphatidylinositol 3-kinase/protein kinase B, MAPK: Mitogen-Activated Protein Kinase, STAT: Signal Transducer and Activator of Transcription, CASP: Caspase, NF-κB: Nuclear factor kappa B, mTOR: mammalian target of rapamycin, TRAF: TNF receptor associated factor, TNF: Tumor Necrosis Factor, IL: Interleukin.

has been further demonstrated that miRNA-34a inhibition protects the liver against IRI [63]. Sodium hydrosulfide (NaHS) pretreatment can also decrease miRNA-34a expression in the hepatocytes and protect hepatocytes from IRI. Overexpression of miRNA-34a further reduces nuclear factor-erythroid 2-related factor-2 (Nrf-2) with downstream target expression [64]. Nrf-2 as a key transcription factor, similarly prevents organs against oxidative-stress-induced damage [65].

1.3.8. miRNA-17

Following reperfusion, the expression of microtubule-associated protein 1 light B II (involved in the formation of autophagosomes) has been gradually up-regulated and peaked at 24 h, a time point associated with maximal miRNA-17 levels. Overexpression of miRNA-17 has correspondingly diminished signal transducer and activator of transcription 3 (STAT3) and phosphorylated STAT3 (p-STAT3) levels, an effect promoting autophagy in response to IRI. It is of note that, STAT3, as a key cellular survival factor, plays an important anti-apoptotic role in response to oxidative stress and appears to be related to miRNA-17 [66].

1.3.9. miRNA-122 & miRNA-148a

The expression levels of miRNA-122 and miRNA-148a, as hepatocyte-derived miRNAs (HDmiRNAs), can be diminished in transplanted liver affected with long warm ischemia. In contrast, the levels of these HDmiRNAs increases in serum, which is positively correlated with serum activity of the liver enzymes such as aspartate transaminase (AST), alanine transaminase (ALT), and lactate dehydrogenase (LDH). Moreover, the serum levels of these miRNAs are enhanced up to be 20-fold during acute rejection, and appear to rise earlier than aminotransferase levels. So, these miRNAs can be used as a very sensitive marker in this condition [67,68].

1.3.10. miRNA-450-5p

The expression of miRNA-450b-5p can be stimulated in hepatic IRI via suppression of Crystallin Alpha B (CRYAB) as its target that lead to increase the inflammatory factors such as IL-1ß, TNF-α, and IL-6. By inhibiting this miRNA, IRI alleviated through restraining nuclear factor κB (NFκB) and activation of Akt/mTOR signaling pathway [69].

1.3.11. miRNA-125b miRNA-125b can be protected liver via inhibiting TRAF6 and NF-κB signal pathway

in hepatic IRI condition. In this way, the expression of TNF-α, IL-1β, and IL-6 was reduced [70].

1.3.12. miRNA-210

During liver IRI and hypoxic condition, miRNA-210 can be increased and lead to inflammation, apoptosis, and cell death by suppression SMAD4 as its target [71].

1.3.13. miRNA-128-3p

The expression level of miRNA-128-3p can be lessen during liver IRI that is negatively correlated with Rnd3 as its target. Due to the increment of this target, the NF-κB pathway and following that inflammatory factors is suppressed and the hepatocytes are protected against IRI [72].

1.3.14. miRNA-142-3p

In the model of hepatic IRI, miRNA-142-3p and its target, myristoylated alanine-rich C-kinase substrate (MARCKS), can be lowered and following that activated p38/JNK signaling pathway, inhibited PI3K/Akt signal, and upregulated NF-κB that lead to inflammation and apoptosis [73].

1.3.15. miRNA-99-5p miRNA-99-5p can be decreased in IRI condition by targeting FGF21 as its target. By overexpression of this miRNA, the expression level of FGF21 upregulates that leads to repress Caspase-3 (CASP-3), lessen oxidative damage and apoptosis and finally attenuates liver injury [74].

1.3.16. miRNA-125b-5p & miRNA-501-3p miRNA-125b-5p and miRNA-501-3p are down regulated and can thus activate the TLR signaling pathway in response to hepatic IRI leading to the increased expression of their target Myd88, c-Fos and A20 that can promote the innate immune response [75].

1.3.17. miRNA-146a miRNA-146a, as one of the most important miRNAs, is a key molecule in inflammatory response [27,76,77]. This miRNA has been identified as a potent negative regulator of the TLR/IL-1α signaling cascades [27,78–80]. In early stage of IRI, the expression of hepatic miRNA-146a is down regulated and this condition is attenuated [81]. In this line, Jiang et al. reported that miRNA-146a could ameliorate liver IRI *in vivo* and H/R injury *in vitro*, through suppressing the activation of NFκB via TLR4 [82].

1.3.18. miRNA-30b miRNA-30b has been down-regulated in mice livers subjected to IR. This miRNA has been accordingly bounded to autophagy related 12 (Atg12) of Atg12-Atg5 complex as proteins required for autophagosome formation. Overexpression of this miRNA can also result in reduced Atg12-Atg5 conjugate levels and inhibit autophagy with subsequent alleviated hepatic IRI [83].

1.3.19. IPC

Hepatic IRI is an inevitable problem occurring in major liver resection and transplantation processes [42]. IPC, which consists of a brief episode of ischemia prior to a prolonged ischemic event, has been shown to protect the liver against IRI in experimental as well as clinical studies [84,85]. In a study, it had been indicated that some miRNAs had changed in response to IPC. Amongst these, four important miRNAs including miRNA-23a, miRNA-326, miRNA-346, and miRNA-370, had been down regulated during IPC, which had been positively correlated with the severity of ischemic injury [86]. The proposed protective mechanism of these miRNAs can be thus associated with MAPK, protein kinase C (PKC), and protein kinase B (Akt) pathway [87–89]. Akt activation associated with hepatic IPC similarly suppresses the activity of several modulators of apoptosis, including the B-cell lymphoma 2 (BCL2) associated agonist of cell death (BAD) protein, glycogen synthase kinase 3 β (GSK3B), and CASP3 [90].

1.4. Renal IRI

Renal IRI is the major cause of acute renal failure, observed in patients suffering from sepsis, ischemic insults such as vascular surgery, and renal transplantation [91,92]. During kidney transplantation, this condition often leads to delayed graft function, renal graft rejection, and permanent impairment of renal function [93]. Several miRNAs have been also recognized to be differentially expressed in renal IRI, which have some physiological and pathological effect by regulation several pathways and have a functional effect on this process (Fig. 2b, Table 2).

1.4.1. miRNA-155

By up-regulating miRNA-155 in IRI condition, CASP1 expression as well as the pro-inflammatory cytokines, IL-1β and IL-18, are increased, resulting in repression of forkhead box O3 (FoxO3a). These events can subsequently lead to renal cell apoptosis [94].

1.4.2. miRNA-24 miRNA-24 is up regulated after IRI in kidney transplant recipients. Enrichment of miRNA-24 also induced renal cell apoptosis, whereas *in vivo* silencing of miRNA-24 in mice following IRI can additionally improve histological tubular epithelial injury, reduce apoptosis, and lower inflammatory cell infiltration with better kidney function. The effect of miRNA-24 can be further mediated through regulation of H2A histone family member X (H2AX), sphingosine-1-phosphate receptor 1 (S1P1), and heme oxygenase-1 (HO-1) as its targets, inducing the deterioration of endothelial tube formation and migration capacity as well as tubular and endothelial cell apoptosis [95].

1.4.3. miRNA-182-5p miRNA-182-5p has been found to be consistently up-regulated after ischemic insults in kidney of human and animal models. Selective *in vivo* inhibition of miRNA-182-5p in IRI model has also improved kidney function [96]. Besides, miRNA-182-5p has reduced the expression of the anti-apoptotic proteins, BCL2, and cell-cycle regulatory cyclin-dependent kinase inhibitors such as p21 and thereby inhibiting cell regeneration [97].

1.4.4. miRNA-17-5p miRNA-17-5p is upregulated during renal IRI and hypoxia in cultured renal tubular cells. Moreover, it can directly inhibit the expression of death receptor 6 (DR6) and attenuate CASP activation and

Table 2 microRNA alteration in renal IRI.

miRNA	Change in IRI	Target(s)	Effect on condition	References
155	Up-regulated	CASP-1, IL-1β, IL-18, FOXO3a	Worsened, Apoptosis	[94]
24	Up-regulated	S1P1, P21	Apoptosis	[95]
182-5p	Up-regulated	Bcl2	Worsened, Apoptosis	[96,97]
493	Up-regulated	STMN-1	Worsened, Fibrosis	[102]
17-5p	Up-regulated	CASP, DR-6	Ameliorate	[98]
687	Up-regulated	PTEN	Ameliorate	[99]
381	Up-regulated	CXCR4, TNF-α	Worsened, Apoptosis	[100]
27a-3p	Up-regulated	PI3K/Akt	Worsened	[101]
211	Down-regulated	SMAD3, TGF-β	Worsened, Apoptosis	[114]
27a	Down-regulated	TLR	Worsened	[115]
204-5p	Down-regulated	Fas/FasL	Worsened	[117]
101	Down-regulated	TGFβ-R1	Worsened, Cell Damage	[118]
126	Down-regulated	SDF1, CXCR4	Worsened	[103,104 106,107
106b-5p	Down-regulated	PTEN, CASP-3	Worsened, Apoptosis	[109,110

S1P1: Sphingosine-1-phosphate receptor 1, Bcl2: B-cell lymphoma 2, STMN: Stathmin, CXCR: C-X-C chemokine receptor, TLR: TGF-β: Transforming growth factor beta, Toll like receptor, PI3K/Akt: Phosphatidylinositol 3-kinase/protein kinase B, CASP: Caspase, PTEN: Phosphatase and tensin homolog, NF-κB: Nuclear factor kappa B, FOXO: Forkhead box O, IL: Interleukin, SDF1: stromal cell- derived factor 1.

apoptosis in cultured renal tubular cells exposed to hypoxia [98].

1.4.5. miRNA-687 miRNA-687 is increased in the kidney during renal IRI and in cultured kidney cells all through hypoxia. It further represses the expression of PTEN, and facilitates cell cycle progression and inhibits apoptosis during hypoxia and renal IR [99].

1.4.6. miRNA-381

In rats with renal IRI, miRNA-381 promotes the proliferation of renal tubular epithelial cells by down-regulating its target, CXCR-4. In fact, kidney IRI is worsened by overexpressed CXCR-4 and subsequently, increased production of TNF-α, enhancement of inflammatory cells, and activation of cell death or apoptosis pathway [100].

1.4.7. miRNA-27a-3p

The expression level of miRNA-27a-3p can be increased in IRI condition by reducing its target, Grb2. In this way, the PI3K-Akt signal and Keap1 down- and up-regulates respectively that result in the exacerbation of the ischemic injury [101].

1.4.8. miRNA-493 miRNA-493 can be up-regulated after hypoxic stress that lead to reduce the expression level of Stathmin (STMN)-1 as cell cycle regulator and increase renal fibrosis [102].

1.4.9. miRNAs-126

Decreased serum levels of miRNA-126 have been shown to predict acute kidney injury (AKI) in ICU patients, correlated with the severity of AKI [103]. Following renal IRI in mice model, the overexpression of miRNA-126 has also displayed a significant improvement of kidney function by increasing endothelial cells and stromal cell-derived factor 1 (SDF1)/CXC chemokine receptor type 4 (CXCR-4), leading to promotion of vascular integrity and supporting the recovery of the kidney after IRI [104–108].

1.4.10. miRNA-106b-5p miRNA-106b has been proven to promote cell proliferation and migration while suppression of this miRNA can reduce these functions, leading to cell cycle arrest and apoptosis [109]. In renal IRI, miRNA-106b-5p has been recognized as one of the most significantly down-regulated miRNAs [110]. Phosphatase and tensin homolog (PTEN) is also known as a candidate target for miRNA-106b-5p [109, 111], playing a critical role in mitochondrial dependent apoptosis [112]. In a study by Yu et al., overexpression of miRNA-106b-5p had dramatically down-regulated the expressions of PTEN in the kidney and had demonstrated fewer apoptotic cells and lower levels of CASP3 activation [113].

1.4.11. miRNA-211

By down-regulation of miRNA-211 in IR condition, TGFβR2 as its target, can be increase. This interaction lead to apoptosis and decrease cell survival via regulation TGFβR2/TGF-β/SMAD3 signaling pathway [114].

1.4.12. miRNA-27a miRNA-27a expression decreases in IRI via up-regulation of TLR4 as its target. Overexpression of miRNA-27a using miRNA-27a mimics effectively inhibit the inflammation and cell death in IRI. Therefore, miRNA-27a may be as therapeutic potential for I/R- induced renal injury [115].

1.4.13. miRNA-124 miRNA-124 expression can be down-regulated in IRI. The over-expression of miRNA-124 lessens the expression of ERS-related proteins via binding to IRE-1α and ultimately attenuate renal IRI [116].

1.4.14. miRNA-204-5p

FasL as direct target of miRNA-204-5p can be up-regulated due to lower this miRNA in renal IRI. By elevation of miRNA-204-5p and negatively regulation of the Fas/FasL pathway, the protective effect of this miRNA is confirmed, which demonstrates the regulatory mechanism of miRNA-204-5p in renal IRI [117].

1.4.15. miRNA-101

In the murine model of renal IRI, the expression level of miRNA-101 lowers and regulates TGFß-R1 as its target. In fact, by overexpression of miRNA-101 with miRNA mimic, the cell damage can be mitigated and it demonstrates this miRNA may be used as a novel therapeutic strategy for this condition [118].

1.4.16. IPC

IPC is a potential renoprotective strategy aimed at boosting tissue tolerance to IRI in a brief period of ischemia and subsequent reperfusion before a major ischemic injury. Although the exact mechanism of IPC remains unclear, nitric oxide [119], PKC [120], MAPK, MAPKAP kinase 2 [121], mitochondria function [122],

and decreased capacity of immune cells [123] have all been suggested as potential mechanisms.

Transient renal IR induced activation of HIF-1α in kidneys can in turn up-regulate miRNA-21 expression at transcriptional level. As well, miRNA-21 can negatively regulate its target effector, proapoptotic gene programmed cell death 4 (PDCD4), as pro-inflammatory protein, and block NF-κB activity and up-regulate anti-apoptotic BCL-2, consequently attenuating inflammation and apoptosis [124,125]. On the other hand, miRNA-21 can inhibit PTEN resulting in activation of PI3K/Akt that can induce the expression of HIF-1α and its target gene, namely, vascular endothelial growth factor (VEGF). Hence, miRNA-21 can indirectly promote HIF-1 stabilization and activity under hypoxic conditions, and act with HIF-1 to form a positive feedback loop [126]. These findings suggest that the protective role of IPC-induced miRNA-21 might be related to its regulatory effects on the PTEN-PI3K/Akt signaling pathway.

2. Conclusion

IRI remains to be a life-threatening clinical issue, resulting in higher rejection rate as well as long-term morbidity and mortality with complex and multifactorial pathogenesis. Understanding the pathways associated with this condition would help lessen the inevitable injury related to this condition. Furthermore, investigation and standardization in the profiling of miRNAs in serum, plasma, and urine samples have been authorized in transplant recipients, to find a robust diagnostic marker and to develop insights into pathways responsible for IRI process as well as novel targets for therapy. Overall, differential regulation of IRI- related miRNAs may lead to improved graft function and survival as well as expansion of donor organ pool.

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Declaration of Competing Interest

The authors report no declarations of interest.

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